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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,452	10/31/2000	David B. Weiner	UPAP-0404	6483

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 12/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/622,452

Applicant(s)

WEINER ET AL.

Examiner

Anne Marie S. Wehbe

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 October 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-7, 9-15, 17-18, 20-22, and 33-36 is/are pending in the application.
- 4a) Of the above claim(s) 20-22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6-7, 9-15, 17-18 and 33-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment and response received on 10/11/04 has been entered. Claims 1-4, 6-7, 9-15, 17-18, 20-22, and 33-36 are currently pending in the instant application. This application contains claims 20-22 drawn to an invention nonelected with traverse in Paper No. 14. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-4, 6-7, 9-15, 17-18, and 33-36 are currently under examination. An action on the merits follows.

The applicant is reminded that the claims under examination has only been examined to the extent that they read on the elected subject matter, i.e. plasmids, and DR5 as the immunomodulatory protein.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Priority

Applicant's amendment to the specification has been entered. Benefit of priority to parent application 60/076,207, filed on 2/27/98, is acknowledged.

Nucleotide and/or Amino Acid Sequences

In view of applicant's amendment of page 31 to insert the appropriate SEQ ID NO., this application is in compliance with the requirements of 37 CFR 1.821 through 1.825.

Claim Rejections - 35 USC § 112

The rejection of claims 1-4, 6-7, 9-15, 17-18, and 33-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that on page 5, the previous office action mistakenly refers to DR5 as an "immunogen". In response, it is noted that the last word in the last sentence on page 5 of the office action mailed on 12/8/03 is a typographical error which should read "immunomodulatory protein". The next sentence in the office action, at the top of page 6 makes clear that the rejection of record is based on the lack of enabling disclosure for the use of DR5 as an "immunomodulatory protein". In fact, pages 6-8 of the office action repeatedly refer to the fact that the specification does not provide sufficient guidance for using DR5 as an "immunomodulatory protein". As such, the rejection of record is clear in stating the office's position that the specification is not enabling for the use of DR5 as an immunomodulatory protein in the context of plasmid vaccines.

The applicant argues that contrary to the office's assertion, there is ample support for DR5 having an immunomodulatory role. However, the applicant has not pointed out where in the specification this "ample support" can be found, or provided any other evidence in the form of a

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declaration or publications from the prior art which show that DR5 has immunomodulatory activity.

The applicant further argues that the office has not provided evidence that contradicts applicant's statement that DR5 is an immunomodulatory protein, citing *In re Marzocchi*. In response, the previous office action provided ample evidence that at the time of filing, the skilled artisan did not consider DR5 as an immunomodulatory protein. Rather, the prior art identifies DR5 as an apoptosis inducing protein. The previous office action stated that DR5, also known as TRAIL-R2 and KILLER, is a death-domain containing receptor which binds to the TRAIL ligand. DR5 was independently cloned by various groups in 1997 (see for instance MacFarlane et al. (1997) J. Biol. Chem., Vol. 272 (41), 25417-25420 and Sheridan et al. (1997) Science, Vol. 277, 818-821). DR5 was not extensively characterized prior to the effective filing date of the instant application. At the time of filing, the art reported that DR5 is a member of a family of receptors that bind TRAIL and which are capable of inducing apoptosis. MacFarlane et al. and Sheridan et al. both reported that ectopic expression of DR5 in certain human cells results in apoptosis and speculate that ligand binding between TRAIL and DR5 may lead to cell death *in vivo* (MacFarlane et al., page 25417, and page 25419, Figure 3; Sheridan et al., page 818, and page 820, Figure 3). The TRAIL/DR5 interaction, however, is further complicated by additional receptors for TRAIL including decoy receptors which appear to inhibit TRAIL mediated signaling through DR5 (Sheridan et al., page 820, Figure 4). Thus, due to the existence of decoy receptors for TRAIL, the skilled artisan would not have been able to predict without undue experimentation whether expression of DR5 in a cell that also expresses a decoy receptor would even result in apoptosis. Summarizing the teachings of the prior art concerning DR5, it appears

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that while the literature at the time of filing does suggest a role for DR5 in regulating cell death, there was no indication that DR5 acts in any way as an “immunomodulatory” protein. DR5 is not preferentially expressed in any type of immune cells and does not appear to have any activity which would result in activation or upregulation of immune responses following antigen exposure. Therefore, based on the nature of DR5 as an inducer of apoptosis, the skilled artisan would not have been able to predict without undue experimentation whether the co-expression of an antigen and DR5 in a cell would in fact be capable of stimulating T cells, B cells, or any other type of immune effector cells. Thus, the office has in fact provided sufficient evidence that the skilled artisan would have a reason to doubt that DR5 could function as an immunomodulatory protein. Thus, the office has in fact met the burden set forth in *In re Marzocchi*.

Further, as discussed in detail in the previous office action, the specification does not provide any guidance which supplements the knowledge present in the prior art concerning DR5. The specification, while listing DR5 among numerous other proteins identified by the specification as “immunomodulatory”, fails to provide any specific description of the activity of DR5, particularly in modulating any immune response, or provide any specific guidance for the generation of any type of immune response following administration of plasmids encoding DR5 and an immunogen. While the specification does in fact provide a number of examples of the broader invention relating to the ability of proteins such as ICAM, LFA-1, and GM-CSF to modulate the immune response to model antigens, the specification does not provide any specific guidance for the use of DR5 as an “immunomodulatory” protein. As discussed in detail above, DR5 is an inducer of apoptosis and does not have any known “immunomodulatory” properties. Further, DR5 is not related structurally or functionally to the immunostimulatory molecules

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exemplified in the working examples such that a correlation can be made between the activity of the cytokines and chemokines utilized in the working examples and DR5. In fact, based on the apoptotic properties of DR5 as reported by Sheridan et al. and MacFarlane et al., the skilled artisan might predict that cells transfected with an antigen and DR5 would undergo apoptosis before they even had an opportunity to engage an immune effector cell, thereby precluding any effect on immune responses to the immunogen. Therefore, in view of the nature of the DR5 molecule as reported in the prior art of record, the lack of particular guidance concerning how to use the DR5 molecule to stimulate or enhance immune responses to immunogen, the lack of working examples which utilize proteins that correlate to DR5, and the breadth of the claims, it would have required undue experimentation to use the invention as claimed.

Finally, the applicant argues that the lack of working examples is not sufficient to reject claims under 35 U.S.C. 112, first paragraph, and states that the specification provides examples using other immunomodulatory proteins such it would be routine for the skilled artisan to use DR5. In response, an analysis of the applicant's working examples was provided in the previous office action and reiterated in the previous paragraph. Further, the rejection of record does not simply reply on the lack of working examples for the use of plasmids encoding DR5 for modulating an immune response. The previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, including 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the instant methods. The working examples in particular were discussed in detail, as was the

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state of the prior art, the nature of the invention, and the predictability of the art. The applicant is also reminded that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Therefore, for the reasons of record discussed in detail above, the rejection of record is maintained.

Claim Rejections - 35 USC § 102

The rejection of claims 1-3, and 12 under 35 U.S.C. 102(a) as being anticipated by MacFarlane et al. (1997) J. Biol. Chem., Vol. 272 (41), 25417-25420, is withdrawn in view of applicant's amendments to the claims to recite that the composition is pyrogen free.

The rejection of claims 1-3, 6, and 12 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,417,328 (7/9/02), hereafter referred to as Alnemri, is maintained. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection of record for reasons of record as discussed in detail below.

The applicant has amended the claims to recite a pyrogen-free composition comprising a single plasmid encoding an immunogen and DR5, and an injectable pharmaceutical solution of the composition. The applicant also claims a pyrogen-free composition comprising a plasmid encoding DR5 and a plasmid encoding an immunogen.

The applicant argues that Alnemri et al. does not teach the limitation that the plasmid or plasmid compositions are "pyrogen-free", and therefore does not anticipate the claims as

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amended. In response, Alnemri et al. specifically teaches the pharmaceutical use of plasmids encoding DR5 to treat disease and further teaches that the pharmaceutical compositions is a sterile aqueous solution that contains no materials in addition to the active ingredients and water or physiological saline (Alnemri et al., columns 22-23, particularly column 23, lines 12-20). Thus, while Alnemri et al. does not specifically use the word "pyrogen-free", Alnemri et al. discloses compositions that are sterile and do not contain material other than the active ingredient, i.e. the plasmid encoding DR5, and water or physiological saline. Such a sterile composition is inherently "pyrogen-free". Therefore, Alnemri et al. does in fact teach compositions which meet the limitations of the claims as amended.

Applicant's amendment has necessitated the following new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6, and 12 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,417,328 (7/9/02), hereafter referred to as Alnemri, in view of U.S. Patent No. 5,693,622 (12/2/97), hereafter referred to as Wolff et al. The applicant claims as amended recite a pyrogen-free composition comprising a single plasmid encoding an immunogen and DR5, and an injectable pharmaceutical solution of the composition. The applicant also claims a pyrogen-free composition comprising a plasmid encoding DR5 and a plasmid encoding an immunogen.

Alnemri teaches a single plasmid encoding the bacterial immunogen beta-galactosidase (lacZ) operatively linked to the RSV promoter and DR5 operatively linked to the CMV promoter (Alnemri, column 27, lines 14-21). Alnemri further teaches a composition comprising two plasmids, where the first plasmid encodes an immunogen such as CrmA or FLAME-1 and the second plasmid encodes DR5 (Alnemri, column 27, lines 14-21, and column 28, lines 47-53). Alnemri also teaches injectable pharmaceutical compositions of the nucleic acids comprising a sterile aqueous solution that contains no materials in addition to the active ingredients and water or physiological saline (Alnemri et al., column 22, lines 12-59, and column 23, lines 12-20).

Alnemri et al. does not specifically recite that the sterile pharmaceutical composition is “pyrogen-free”. However, at the time of filing, the skilled artisan would have understood that a sterile composition is “pyrogen-free” and/or that the standard method of preparation of plasmid

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DNA for injection included purification steps which remove bacterial contaminants. Wolff et al. supplements Alnemri et al. by teaching that the preparation of sterile plasmids for injection included the removal of bacterial contaminants. Specifically, Wolff et al. teaches that a plasmid encoding a gene of interest for injection into a human or mammals is purified by the standard method of cesium chloride centrifugation to remove bacterial contamination and resuspended in sterile pyrogen free water (Wolff et al., column 44, lines 19-26, columns 24-25, example 4, and column 19, lines 51-58). Thus, in view of teachings of Alnemri et al. to prepare a sterile pharmaceutical composition comprising a plasmid(s) encoding DR5 for administration to a mammal, and the teachings of Wolff et al. for standard methods of preparing plasmid DNA for in vivo administration, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the standard methods taught by Wolff et al. to prepare the plasmids encoding DR5 and an immunogen taught by Alnemri et al.. Further, based on the standard nature of cesium chloride purification, and the high level of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in producing a pyrogen-free composition containing the plasmid(s) taught by Alnemri et al. using the purification method taught by Wolff et al.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

